August 30, 1973

Dr. Marvin O. Maul
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Dear Dr. Maul,

I have your letter of August 28th asking for comments on the FDA draft regulations on assay methods for residues.

Much as I felt I had cause to complain about the AHI task force approach to these problems, the scientific premises of these draft regulations are totally illusory. In my view the AHI committee would have much to criticize but as I think you will already have perceived I feel they have misdirected their energies.

I am of course referring to the concept of zero tolerance, no residue. By deciding which methods are acceptable, the FDA is of course begging the question of regulating a residue to that level which is socially acceptable. (Note that I did not say as zero risk).

The subheading Exogenous Compounds is fraught with internal contradictions about the objective intended to be accomplished; presumably these will be resolved by the exercise of regulatory judgment under the heading of "The Intended Use Pattern of the Compound". The real objective evidently is to minimize overall public exposure to potentially carcinogenic compounds. The FDA simply cannot logically escape from its dilemma that it is de facto determining levels of dissemination which it has concluded to be socially acceptable.

But later on the regulations take on a much more reasonable tone which at least permit one to examine the premises of the proposal.

The basic arguments seems to be that the risk be held to a level of 1/100 million; however, this is to be estimated so conservatively that the probable risk on the basis of the assumptions presented is of the order of 1/billion. Whether this is an appropriate level in the light of risks involved in other procedures, and of the expected benefits from a new additive is a social policy consideration that doubtless deserves greater debate. But at least for the first time the assumptions are exposed and this is an enormous advance. (I should think that for most additives for which there were a sufficient market to wish to pursue the question that these risks are far too conservative perhaps by two or three orders of magnitude.)

Nevertheless I would strongly support the validation of this approach to regulatory standards as it is the only one that is likely to lead to rational social policy responses. Plainly, it is quite inconsistent with the language of the preamble!

One item, marked 3 in my copy, that makes these assumptions possibly less conservative, is the standardization by body weight. Since one cancer is enough to kill a 150 kg man as readily as a 25 gram mouse this may be loading the scales towards underestimating the human risk if we assume that the 2 species are unknown to be different in sensitivity.

Paragraph 4 seems to verify that the language of this regulation is intended to provide a meaningful definition of "no residue".

The subheading Endogenous Compounds seems very reasonable -- if anything it may be too liberal in a way that shows the limitations of trying to solve problems of risk by regulation. The FDA would find it difficult to justify prohibitions that were directed at risks no different from 1% of normal animals, in spite of the fact that 1% of normal animals quite conceivably are generating levels of hormone that we would be better not to take in. However, in the absence of any concrete example of such a phenomenon among life-stock there is no point pursuing this issue and I suggest you just give this entire section your wholehearted stamp of approval. Once again I would recommend taking a few mild knocks, although I imagine it may even be to Syntex's own advantage, in order to help rationalize the overall procedure which I think this section does.

The heading Assay Evaluation Criteria I find rather difficult to read and understand. Perhaps other documents contain the definition of "sensitivity" of assay methods. I should have thought that one would want to have sensitivities that were capable of measuring with some precision whether the level of residue was below or above the regulatory action level. If that is what is meant by sensitivity then my remark can be withdrawn. Or perhaps they are waffling, for the sake of taking a rational position, against the legal requirement of zero residue. The language about residues being two positives or not suggests that interpretation.

Summary line 2 also appears to be an answer to my question.

The word drug seems to have krept in at mark 5 -- I leave that to you for legal analysis.

All of this seems to be preamble. In the actual draft regulation text the Mantel Bryan extrapolation is mentioned but no social criterion, like one per 100 million is explicitly mentioned. Again this may require some legal analysis to determine whether this makes a difference, whether it leaves it to the discussion of the FDA without further procedures to change that objective criterion.

Very important and very encouraging is item 6. For the first time it would seem to be possible to introduce other relevant data to refute prima facie evidence of carcinogenicity levels as determined in some particular animal. It may then be possible to rebut experiments that are done on hypersensitive bitches for example provided that one can obtain relevant experimental information to justify adjusting the parameters from that special experiment. It is not clear who will have the final responsibility of determining whether the data indicate the applicability of other methods of extrapolation, and this may be the main point that I would recommend you consider further in your comments on the proposal.

By and large the actual language of the new regulation seems to me a considerable improvement over current practice, and one that one might hope might be extended to other areas like food additives and drugs in clinical testing. Some of the explanatory and introductory language is self-contradictory but this may represent the efforts of some reasonable man within the agency trying to find formulations consistent with the letter of the law on the one hand and with the possibility of scientific validation on the other.

I do not intend to make any personal filing on this matter. Needless to say, please feel free to use any of the arguments that I have communicated here but I trust you will consult me before they are attributed to me.

Sincerely yours,

Joshua Lederberg
Professor of Genetics

JL/rr
Enclosure